REMARKS

Applicant respectfully requests entry of amendments to claims 1, 8, 16-18, 24, 25, 32, 39-41, 44, 45, and 47. Please cancel claims 2, 15, 20, 26, 42, and 43. Support for the amendments can be found throughout the specification, including paragraphs [0081], [0089]-[0095], Figures 1-5, and the originally filed claims and, therefore, do not add new matter.

Applicant submits that pending claims 1, 3-14, 16-19, 21-25, 27-41, and 44-52 are in condition for allowance, and respectfully requests that the claims as amended be entered.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1, 3-14, 16-19, 21-25, 27-41, and 43-52 and stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. As claim 43 has been canceled, the rejection as applied to this claim is rendered moot.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Claims 1, 25, and 45 no longer recite "intermediate construct," so the rejection is rendered moot. Applicant has amended the claim to recite "chimeric constructs" which when recombined produce the "third DNA construct." The term "chimeric" is a term of art and would be known to one of skill in the art generally as fabricated DNA of diverse genetic constitution. Further, as the chimeric DNA constructs are used to generate the third construct, one of skill in the art would be able to differentiate the separate constructs. As such, one of skill in the art would understand the metes and bounds of the claims.

Regarding claim 7, while Applicant does not acquiesce to the reasoning offered in the Office Action, and to expedite prosecution toward allowance, claim 7 has been amended to be dependent from claim 6. As such, the antecedent basis issue is moot.

For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Rejections Under 35 U.S.C. §102

Claim 41 stands rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Shiao et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the cited reference teaches the elements as recited in the present claims. However, the reference is limited to glucagon receptor.

The present claim does not recite metabolic pathway genes.

As stated in Hybritech Inc. v. Monoclonal Antibody, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986), "It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention."

Therefore, because the instant claim does not recite a metabolic pathway gene, the cited reference does not anticipate the claimed invention.

Failure of the prior art to meet every element of the claimed invention does not meet the standard under §102. For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Claims 41, 47, 49, and 50-52 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Divoky et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the cited reference teaches the elements as recited in the present claims. However, the reference is limited to human erythropoietin receptor. Further, Divoky et al. do not teach or suggest constructs comprising human-non-human animal DNA sequences which are bacterial artificial chromosomes (BAC) (i.e., only that homologous sequences flanking site were derived from BAC, not that human mouse constructs were comprised in a BAC; see, p.986, col. 2).

The present claims do not recite a cell signaling pathway gene. However, they specifically recite that constructs comprising human and non-human DNA sequences are BAC constructs.

As stated in Hybritech Inc. v. Monoclonal Antibody, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986), "It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention."

Therefore, because the instant claims do not recite a cell signaling pathway gene, and expressly recites BAC constructs as claimed, the cited reference does not anticipate the claimed invention.

Failure of the prior art to meet every element of the claimed invention does not meet the standard under §102. For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Rejections Under 35 U.S.C. §102/103

Claims 1, 8, 16, 17, 25, 32, 34, 39, 40, 45, and 46 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as being obvious over Shiao et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicant submits that because the cited reference does not teach all the claim limitations, no *prima facie* case has been established.

As stated by U.S. Court of Appeals for the Federal Circuit in In re Brouwer (37 U.S.P.Q.2d 1663 (Fed. Cir. 1995)):

> "The test of obviousness *vel non* is statutory. It requires that one compare the claim's 'subject matter as a whole' with the prior art 'to which said subject matter pertains.' 35 U.S.C. Section 103. The inquiry is thus highly fact-specific by design. This is so 'whether the invention be a process for making or a process of using, or some other process.'"

Further, the court stated that, "the mere fact that a device or process utilizes a known scientific principle does not alone make that device or process obvious." (Id., at 1666).

In Brouwer, the Applicant claimed a process against which the Examiner cited a generic teaching for a chemical reaction using a similar active compound to generate a specific resin. The Examiner provided no suggestion or motivation as to why one of skill in the art would modify the methods as recited in the applied art to achieve the invention as claimed and failed to compare specific differences between the claimed invention "with all of its limitations" and the prior art reference (Id.). The court held that the because the Examiner failed to rely on particularized findings, as required by Graham, the Examiner was in error (Id.).

For the present set of facts, the Office Action states that "since the recited 'recombining' embraces any means (such as the enzymatic method taught by Shiao et al.), and numerous steps of recombining leading to the construction of a final targeting vector, and since the process of making the final genetic construct as taught by Shiao et al. comprise a serial of steps and constructs which could have been considered as the first, second, third, and the final (fourth) constructs before it is introduced to the mouse ES cells" the claimed invention as a whole was at least prima facie obvious, if not anticipated. Based on this argument, Applicant submits that the explicit process steps as claimed have been disregarded, and when express process steps are not considered, the analysis has failed to consider the subject matter as a whole (see, e.g., M.P.E.P. §2141.02(II)), as such, the Graham factors have not been considered. Also, the Action basically argues that the mere fact that the process utilizes a known scientific principle alone makes the claimed process obvious. In view of In re Brouwer, such a rejection is improper, and thus, the burden of establishing a *prima facie* case of obviousness has not been met.

Further, because the expressly recited first, second, chimeric, and third constructs are not taught or suggested in Shiao et al., the reference does not teach all of the elements as claimed, thus, the method as claimed would not have the properties sought by Applicant, and one of skill in the art would not have an expectation of success since the invention as claimed would not be achieved in view of such teachings. Therefore, the claims are not obvious in view of such a reference. Moreover, because the expressly recited first, second, chimeric, and third constructs

are not taught in Shiao et al., the reference, in the alternative, does not anticipate the invention as claimed.

It is axiomatic that one cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Therefore, in view of a) the failure to properly analyze the claims because the specific claim elements (positive process steps) were disregarded and b) the failure of the reference to teach or suggest all of the elements as claimed, the Action is in error with regard to anticipation, or in the alternative, obviousness, because no *prima facie* case has been established.

For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claims 1, 3, 8, 10, 11, 13, 14, 16, 17, 25, 27, 32, 34, 35, 37, 39, 40, and 45 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as being obvious over Divoky et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicant submits that because the cited reference does not teach all the claim limitations, no *prima facie* case has been established.

As stated by U.S. Court of Appeals for the Federal Circuit in In re Brouwer (37 U.S.P.Q.2d 1663 (Fed. Cir. 1995)):

> "The test of obviousness *vel non* is statutory. It requires that one compare the claim's 'subject matter as a whole' with the prior art 'to which said subject matter pertains.' 35 U.S.C. Section 103. The inquiry is thus highly fact-specific by design. This is so 'whether the invention be a process for making or a process of using, or some other process.'"

Further, the court stated that, "the mere fact that a device or process utilizes a known scientific principle does not alone make that device or process obvious." (Id., at 1666).

In Brouwer, the Applicant claimed a process against which the Examiner cited a generic teaching for a chemical reaction using a similar active compound to generate a specific resin. The Examiner provided no suggestion or motivation as to why one of skill in the art would modify the methods as recited in the applied art to achieve the invention as claimed and failed to compare specific differences between the claimed invention "with all of its limitations" and the prior art reference (Id.). The court held that the because the Examiner failed to rely on particularized findings, as required by Graham, the Examiner was in error (Id.).

For the present set of facts, the Office Action states that "since the recited 'recombining' embraces any means (such as the enzymatic method taught by Divoky et al.), and numerous steps of recombining leading to the construction of a final targeting vector, and since the process of making the final genetic construct as taught by Divoky et al. comprise a serial of steps and constructs which could have been considered as the first, second, third, and the final (fourth) constructs before it is introduced to the mouse ES cells" the claimed invention as a whole was at least prima facie obvious, if not anticipated. Based on this argument, Applicant submits that the explicit process steps as claimed have been disregarded, and when express process step are not considered, the analysis has failed to consider the subject matter as a whole (see, e.g., M.P.E.P. §2141.02(II)), as such, the Graham factors have not been considered. Also, the Action basically argues that the mere fact that the process utilizes a known scientific principle alone makes the claimed process obvious. In view of In re Brouwer, such a rejection is improper, and thus, the burden of establishing a *prima facie* case of obviousness has not been met.

Further, the Action states that the initial mouse genomic sequence is carried by a bacterial artificial chromosome, citing col. 2, p. 986. This misinterprets the instant claim elements, the reference expressly states that only homologous sequences flanking the gene were derived from BAC, the claims recite a construct having human and non-human sequences which comprise a BAC. Moreover, Divoky et al. require the use of double replacement gene targeting (see, p. 987, col. 1, "Homologous Recombination in ES cells and Generation of hEPOR Knock-In Mice," col. 2, "Results and Discussion" (tag and exchange); and p. 988, Fig. 1). Divoky et al. teach that the ES cell is first contacted with a targeting vector to insert a positive selectable marker into ES cells. The "tagged" cells are then used to produce offspring, and those animals showing germ

line transmission for the positive marker are used to produce cell lines for a second targeting vector (exchange). No such tag and exchange are cited or required in the present method.

Applicant submits that, in fact, the cited reference "teaches away" from the present invention. One of skill in the art would only extract from such a teaching that the making of humanized mice cannot be accomplished in the absence of "tag and exchange." As such, the reference does not teach the purpose of direct humanization of mice as claimed, and thus, the purpose of Applicant's invention could not be accomplished using the teachings of the cited reference. Therefore, the reference teaches away, since the impression left to the skilled artisan is that the method would not have the property sought by Applicant. In re Caldwell, 319 F.2d 254, 256, 138 U.S.P.Q. 243, 245 (CCPA 1963).

Applicant submits, not merely as a theoretical proposition, that because tag/exchange is ultimately recited *as a requisite property* of the method of Divoky et al., direct humanization of mouse cells is an impossibility.

Further, because the expressly recited first, second, chimeric, and third constructs are not taught or suggested in Divoky et al., the reference does not teach all of the elements as claimed, thus, the method as claimed would not have the properties sought by Applicant, and one of skill in the art would not have an expectation of success since the invention as claimed would not be achieved in view of such teachings. Therefore, the claims are not obvious in view of such a reference. Moreover, because the expressly recited first, second, chimeric, and third constructs are not taught in Divoky et al., the reference, in the alternative, does not anticipate the invention as claimed.

It is axiomatic that one cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Therefore, in view of a) the failure to properly analyze the claims because specific claim elements (positive process steps) were disregarded, b) the failure of the reference to teach or suggest all of the elements as claimed, and c) because Divoky et al. teach away from the present invention, the Action is in error with regard to anticipation, or in the alternative, obviousness, because no *prima facie* case has been established.

For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claims 4-7, 9, 12, 18, 19, 21-24, 28-31, 33, 36, 38, 41, 47, and 48 stand rejected under 35 U.S.C. §103(a) as being obvious over Divoky et al. in view of Heintz et al., and as evidenced by Chrast et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicant submits that because the cited reference does not teach all the claim limitations, no *prima facie* case has been established.

The deficiencies identified in Divoky et al. have been identified above, and will not be reiterated here. The Office Action alleges, in pertinent part, that Divoky et al is silent with respect to use of a BAC targeting construct and *E. coli* in all steps of the recombining process. The Action then provides Heintz et al. to cure the deficiency identified in the primary reference. Heintz et al. teach the following:

> "This method and **all** subsequent methods that have been reported to rely on three basic features (FIG.1). First, competence for homologous recombination is restored to the BAC host strain by reintroduction of the *E. coli recA* gene, or by the introduction of another enzyme that can restore to the BAC host the ability to perform homologous recombination. Second a shuttle vector (or DNA fragment) that carries the desired reporter gene or modified cassette, flanked by sequences homologous to the genomic DNA carried in the BAC, is used to target the modification cassette into a precise site on the genomic DNA insert. Appropriate recombinants are selected and screened for precise co-integration into the targeted site on the BAC DNA. Third, unwanted vector sequences are resolved through a second homologous recombination event, or excised from the co-integrants using an appropriate site-specific recombinase. Negative selection is used to enrich the desired end product – a BAC that carries the modification cassette inserted into the exact position chosen in the design of the experiment." (p. 862, col. 1, second paragraph). (Emphasis added)

This is in contrast to the present invention, which, *inter alia*, does not restore *recA* by introduction of *recA* or by introduction of another enzyme that can restore homologous

recombination, nor does the present invention use a second vector that carries the desired gene.

The present specification at paragraphs [0118] to [0122] states:

> "[0118] Using BAC technology the entire mouse PXR coding region will be replaced with the corresponding human PXR coding region (including introns) by homologous recombination. Human PXR gene expression will be detected in the transformed mice by Northern analysis and PCR. Particular attention will be made to determine whether human PXR is expressed in liver and gastrointestinal tract, and other tissues that normally express the receptor in humans. This will distinguish this approach from any other transgenic procedures used to express human PXR in mice.
>
> "[0119] First, an E. coli host is needed that has certain characteristics that allow stable propagation of large mammalian DNA inserts in the BAC vector, and is able to selectively carry out proper homologous recombination when needed. The strain HS996, which will be used for these studies, has been constructed to accommodate large BAC inserts, and its $recA^+$ derivative HS985 has been chosen as a founder strain for further modification. This strain has been modified to perform conditional homologous recombination; cells will become proficient in recombination only when cells are grown at 30°C.
>
> "[0120] The relevant genotypes of HS985 for the work are: RecB21, recC22, sbcB15, sbcC201, $mcrA^-$, del(mrr-mcrBC), and endA1. Mutations in RecB, C and endA1 allow E. coli to protect incoming linear DNA from degradation. Mutations in sbcB and C inhibit degradation of DNA having hairpin structure. Mutation in $mcrA^-$ and del(mrr-mcrBC) remove the host restriction-modification system, therefore mammalian DNA is not degraded.
>
> "[0121] RecAts200 is a temperature sensitive mutant for generalized recombination. Mutation of recAts200 has been introduced to HS985 by P1 transduction. Phage P1 grown in a strain carrying recAts200 has prepared and infected into HS985 to obtain recombinant clones having the phenotype of temperature sensitive recombination. The resultant strain HS2001 has been further tested to confirm the genotype of HS985.
>
> "[0122] HS2001 is defective in recombination at high temperatures (40° C.) whereas at lower temperature (30° C.) it is capable of carrying out recombination normally. For the BAC DNA transfection studies, electrocompetent HS2001 prepared at 30° C. is used and the transfected cells are allowed to grow at 30° C. until the recombination is finished, and then raise the temperature to 40° C. to prevent unwanted recombination events, which can include the formation of deletions and rearrangement due to repeated DNA sequences often found in mammalian DNA."

As can be seen from the specification, none of the required steps recited in Heintz et al. were used to develop the BAC-human construct as claimed (see, e.g., paragraph [0121]). Further, Heintz et al. specifically warns against the use of PCR to in assembling BAC cassettes (see, p. 862, col. 2, first paragraph). In contrast, the present specification expressly uses PCR to achieve the invention as claimed (see, e.g., paragraphs [0089] to [0091], and Figs. 1A, 1B, 1C, 5A, 5B, and 5C).

Applicant submits that, in fact, the cited reference "teaches away" from the present invention. One of skill in the art would only extract from such a teaching that the making of humanized mice cannot be accomplished in the absence of the steps as recited in Heintz et al., nor in conjunction with PCR. As such, the reference does not teach the purpose of direct humanization of mice as claimed, and thus, the purpose of Applicant's invention could not be accomplished using the teachings of the cited reference. Therefore, the reference teaches away, since the impression left to the skilled artisan is that the method would not have the property sought by Applicant. In re Caldwell, 319 F.2d 254, 256, 138 U.S.P.Q. 243, 245 (CCPA 1963).

Applicant submits, not merely as a theoretical proposition, that because the specific steps and caution against PCR are ultimately recited *as a intrinsic property* of the method of Heintz et al., the method as claimed is an impossibility. Further, as there is no suggestion or expectation of success regarding the present invention in view of Divoky et al. and/or Heintz et al. as claimed whether Chrast et al. teach linearized BAC as a mid-product during BAC preparation is immaterial.

Again, it is axiomatic that one cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Since the teachings of Divoky et al. would not result in the claimed invention when combined with the teachings of Heintz et al. and/or Chrast et al., one of skill in the art would not have an expectation of success since the invention as claimed could not be achieved in view of such teachings. Therefore, one of skill in the art would not be motivated to combine such teachings.

Therefore, in view of a) the failure to properly analyze the claims because specific claim elements (positive process steps) were disregarded, b) the failure of the reference to teach or suggest all of the elements as claimed, and c) because Divoky et al. and Heintz et al. each, alone and in combination, teach away from the present invention, there is no reasonable expectation of successfully achieving the invention as claimed, thus, no *prima facie* case for obviousness exists. For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Claims 4-7, 9, 12, 18, 19, 21-24, 28-31, 33, 36, 38, 41, 43, 44, 47, and 48 stand rejected under 35 U.S.C. §103(a) as being obvious over Divoky et al. in view of Heintz et al, and in further view of Xie et al. As claim 43 has been canceled, the rejection as applied to this claim is rendered moot.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Applicant submits that because the cited reference does not teach all the claim limitations, no *prima facie* case has been established.

The deficiencies identified in Divoky et al. and Heintz et al. have been identified above, and will not be reiterated here. The Office Action alleges, in pertinent part, that Divoky et al. and Heintz et al. are silent with respect to specifying PXR. The Action then provides Xie et al. to cure the deficiency identified in the primary references.

Review of Xie et al. shows that the transgenic animals comprising the PXR gene were not created by homologous recombination, and in fact, the transgenic animals are generated using cDNA and vectors comprising sequences from mouse albumin promoter/enhancer and SV40 intron polyA sequences (p. 438, col. 2, "Generation of transgenic mice"). As such, there would be no PXR non-coding regions at the 3' and 5' ends which would allow for homologous recombination. Further, as the vectors comprise cDNA, there are, for example, no introns available, thus, there would be a lack of available expression control signals for appropriate induction/suppression of expression in particular cells. Therefore, while Xie et al. may or may not teach transgenic mice comprising PXR, they do not teach homologous recombination

between mice an human DNA sequences that have the same relative order when such sequences are present in the genome of a human (i.e., comprise intronic sequences).

Again, it is axiomatic that one cannot simply use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Since the teachings of Divoky et al. would not result in the claimed invention when combined with the teachings of Heintz et al. and/or Xie et al., one of skill in the art would not have an expectation of success because the invention as claimed would not be achieved in view of such teachings. Therefore, one of skill in the art would not be motivated to combine such teachings.

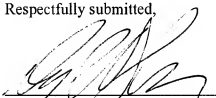
Therefore, in view of a) the failure to properly analyze the claims because specific claim elements (positive process steps) were disregarded, b) the failure of the reference to teach or suggest all of the elements as claimed, c) because Divoky et al. and Heintz et al. each, alone and in combination, teach away from the present invention, and d) the failure of Xie et al. to teach or suggest homologous recombination or, by virtue of using cDNA, teach DNA sequences having the same relative order of sequences present on a human genome, there is no reasonable expectation of successfully achieving the invention as claimed, thus, no *prima facie* case for obviousness exists. For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Conclusion

Applicant submits that pending claims 1, 3-14, 16-19, 21-25, 27-41, and 44-52 are in condition for allowance. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this submission.

Please charge Deposit Account No. 07-1896 in the amount of $230.00 to cover a Two Month Extension of Time fee. The Commissioner is hereby authorized to charge any additional fees required by this submission, or make any credits or overpayments, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,



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